MEDICINAL CHEMISTRY VI

Proceedings of the 6th International Symposium on Medicinal Chemistry, Brighton, U.K. September 4-7, 1978

A. SIMKIN
(Editor)

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MAIN LECTURES

Editor. M. A. SIMKINS

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FOREWORD

The papers given at the VIth International Symposium on Medicinal Chemistry and collected in this volume were chosen by members of the Society for Drug Research.

In recent years it has become increasingly apparent that Medicinal Chemistry cannot be usefully carried out unless the chemist works in close association and harmony with a biologist. To that end the successful medicinal chemist is one who has acquired a working knowledge of the basic pharmacology fundamental to the area in which he is working; this aspect, along with a detailed awareness of structure activity relationships, is the mainspring of success in the discovery of new and better medicines.

Reflecting this need the Society for Drug Research includes pharmacologists, physicians, physical chemists and others besides the medicinal chemist among its members. It was therefore almost predictable that, when the opportunity for choice was afforded the Society, the presentations made at the VIth International Symposium on Medicinal Chemistry would cover a similar spread of interest.

The three Plenary Lectures published in this volume represent the ideas of eminent men, two of them Nobel Laureates. Dr. Pauling speaks of a new concept in therapy, that of orthomolecular medicine, a complete reversal of recent trends where major emphasis has been placed upon achieving ever greater potency in a molecule. Sir John Cornforth proposed a greater awareness of the structural chracteristics of enzymes while Sir Arnold Burgen showed how modern techniques can determine our understanding of receptors.

The papers presented in the various symposia were a blend of biology, chemistry, biochemistry and medicine all directed towards specific ends. While the majority of the symposia were based on disease states some were completely theoretical relating to the interaction of substrate and receptor or the prediction of activity of molecules on structural grounds alone.

It is hoped that by publication of these papers an audience much wider than those scientists who were fortunate enough to attend the meeting at the University of Sussex will find benefit. Moreover the eminence of the speakers and the quality of their presentations deserve the permanent record this volume affords.

J.F. Cavalla
Chairman, Organising Committee

M.A. Simkins
Editor

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ASCORBIC ACID IN RELATION TO DISEASE

Linus Pauling

Linus Pauling Institute of Science and Medicine
2700 Sand Hill Road, Menlo Park,
California 94025, U.S.A.

Ascorbic acid (sodium ascorbate, vitamin C) has been found to be of value in the control of various diseases.

I became interested in ascorbic acid and other vitamins about thirteen years ago. In the 1930's I had worked on the magnetic properties and other properties of hemoglobin and hemoglobin derivatives and also in the field of immunochemistry. Then for about ten years, beginning in 1945, my students and I worked on sickle-cell anemia and other hereditary hemolytic anemias, which we classed as molecular diseases. Then in 1954 we began work on mental diseases, to see to what extent they could be described as molecular diseases. At about the end of the ten-year period devoted to this work I became aware of the publications of Abram Hoffer and Humphry Osmond, in Saskatoon, Saskatchewan, Canada, on the treatment of acute schizophrenia by giving the patients large doses of nicotinic acid or nicotinamide. The doses might be as large as 17,000 milligrams per day, one thousand times the usually recommended daily intake, which suffices for most people to prevent the development of the deficiency disease pellagra. I was astonished that such large intakes would be given. I found on checking the literature that there were reports also that patients with mental diseases had benefited from very large doses of ascorbic acid and of other vitamins.

These facts caused me to propose the use of the adjective "orthomolecular" to describe treatments of this sort. Orthomolecular medicine may be defined as the achievement and preservation of the best of health and the prevention and

treatment of disease by using substances that are normally present in the human body; this is, by achieving the presence in the human body of the right molecules in the right amounts. The right molecules are those of the substances that are normally present in the human body, often being required for life, such as the vitamins and also other substances, such as insulin, that are synthesized in the body.

The possibility of a great variation in concentration of ordinary drugs in the body fluid is ruled out by their toxicity. Most of the drugs are effective against disease only when they are used in an amount that comes close to the lethal dose. These drugs in general are rather toxic, and their toxicity limits the amounts that can be ingested. Most of the vitamins, however, are remarkably lacking in toxicity and in serious side effects. Ascorbic acid, for example, has been taken in amounts as large as 200 grams in a space of a few hours by an adult human being, who did not experience any significant side effects from this dosage, and 125 grams of sodium ascorbate has been administered intravenously to a patient within a ten-hour period, with benefit rather than harm. These amounts are about 25,000 times the daily amount needed to prevent pellagra. There is accordingly the possibility of searching for the optimum intake of a vitamin such as vitamin C over a tremendous range of concentrations. The low toxicity of most vitamins, in comparison with drugs, and the possibility of varying the dosage over a wide range constitute the major differences between the substances used in orthomolecular medicine and those used in toximolecular medicine.

One question that we may ask is that about what might be considered the normal physiological intake of ascorbic acid. It is remarkable that human beings and other primates are among the extremely few species of animals that require exogenous ascorbate. The amounts manufactured by animals of various

species have been determined. These amounts are proportional to body weight, and correspond to the intake of ten grams of ascorbic acid per day by a 70-kg man. Various other arguments support the conclusion that about ten grams of this vitamin is a normal physiological amount, per day.

Ascorbic acid in large doses has been found to be of value in the control of various infectious diseases, including viral diseases. An example is hepatitis. Morishige and Murata have reported that a high intake of ascorbic acid, two grams per day or more, provides complete protection against serum hepatitis (hepatitis B) in patients who have received transfusions of whole blood. In their most recent report they described a series of 1285 surgical patients who had received transfusions, without a single case of hepatitis B. These patients had received between two grams and ten grams of ascorbic acid per day. The incidence of serum hepatitis in other patients who received transfusions of whole blood, without the benefit of the protection by ascorbic acid, is between 7% and 10% in the same hospital and in other hospitals in the same region of Japan.

Vitamin C has also been reported to be of benefit to patients with advanced cancer, and to have prophylactic value in decreasing the incidence of cancer. Ewan Cameron and his collaborators have found that patients with advanced cancer who received ten grams of ascorbate per day lived on the average 300 days longer than similar patients who were treated in the same way in the same hospital and by the same physicians, except that they did not receive the ascorbate. Moreover, the patients who served as matched controls did not survive longer than fifteen months, whereas eight of the 100 ascorbate-treated patients are still alive, after as much as seven years after being deemed to be in the terminal state of the disease.

It is the opinion of Cameron and me that the principal mechanism of action of the increased intake of the ascorbate is through making the natural protective mechanisms of the body more effective. It is known that vitamin C is essential to maintain the integrity of the ground substance that serves as the intercellular cement, and for the synthesis of the collagen fibrils that strengthen the ground substance. It is also involved in several ways in the immune mechanism. It has recently been reported that an intake by human beings of large amounts of vitamin C increases greatly the rate of production of lymphocytes under antigenic stimulation. The volunteers who received 5 g per day for three days showed a doubling of the rate of blastogenesis of lymphocytes, those who received 10 g showed a tripling, and one who received 18 g per day for three days showed a quadrupling of this rate. It is well established that a high rate of lymphocyte blastogenesis is associated with a favorable prognosis in cancer.

It is the opinion of Dr. Cameron and me that a significant decrease in the age-specific incidence of and mortality from cancer can be achieved by proper use of vitamin C, and that additional benefit might well result from use also of other orthomolecular agents.

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SPATIAL COMPULSIONS OF ENZYMES

J.W. Cornforth
University of Sussex
Brighton, England

By studying chemical reactions in solution, organic chemists have slowly accumulated a large body of information on reactions which notionally might give more than one isomer or stereoisomer but in fact yield products in which a particular species predominates. Several effects have been recognized as contributing to these results; three of the most important can be briefly designated as mechanism, repulsion and proximity.

The importance of mechanism in determining the position of attack by a reagent on a molecule was recognized quite early and the attention of chemists was directed to it by such phenomena as the Walden inversion and the positional specificity generalized in Markovnikov's rules. For our purpose a good example is the specific behaviour of E- and Z-2-butenes with hypobromous acid: two different bromohydrins, differing only in stereochemical arrangement, are produced without detectable overlap. This is the consequence of a mechanism in which one side of the double bond is occupied by a bromine atom in a complex that does not permit rotation about the carbon-carbon bond before the reaction is completed by attack of a water molecule on the opposite, unoccupied side.